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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,877	PFEIFFER ET AL.	
	Examiner	Art Unit	
	James (Doug) Schultz, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *18-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *originally* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *see action*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-17 in the reply filed on July 6, 2010 is acknowledged. The traversal is on the ground(s) that all of the remaining claims and groups depend from claim 1, and as such should be examined together. This is not found persuasive because the fact that all claims depend on claim 1 is not in and of itself a sufficient reason for preventing restriction. It is granted that claim 1 embraces all groups and is properly considered a linking claim, and that allowance of claim one would cause rejoinder of all groups embraced by the allowed linking claim; however, claim 1 nevertheless links multiple inventions that are properly restrictable, for reasons provided in the restriction requirement. Applicants have provided no legal justification supporting their conclusion that all claims dependent from a single claim are so linked as to be unrestrictable. The requirement is still deemed proper and is therefore made FINAL.

Claims 18-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 6, 2010.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the

reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The disclosure contains sequences which fall under the purview of 37 CFR 1.821 through 1.825 as requiring SEQ ID NOS:, but which are not so identified. For example, at at least page 7 of the instant specification, several nucleotide sequences in excess of 10 nucleotides long are disclosed, and not identified by a SEQ ID NO:. Applicants should be aware that these sequences may not be the only instances necessitating this notice. Applicants should carefully review the application for any further examples of failures to identify any sequences by SEQ ID NO:, and to otherwise verify that the application is in compliance.

Applicant is required to comply with all sequence rules set forth in 37 CFR 1.821 through 1.825 in the next substantive response. This requirement will not be held in abeyance, and failure to comply with these requirements may result in ABANDONMENT of the application under 37 CFR 1.821(g). Direct the reply to the undersigned. Please note that any sequences not already disclosed in a CRF will require amendment and resubmission of a new CRF and sequence listing.

Information Disclosure Statement

The information disclosure statements (IDS's) submitted on August 28, 2006, and August 25, 2009 were filed before the mailing date of the instant first action on the merits. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner, and signed and initialed copies are enclosed herewith.

Claim Objections

Claim 3 is objected to for misspelling the word "hybridized" in the second line of said claim. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-9, 11, 14, 15, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-8, 11, 14, 15, and 17 all recite "an oligonucleotide" which has at least a first and second strand. However, the specification recites at page 3, 2nd paragraph: "As used herein the term 'oligonucleotide' refers to a short length of p single-stranded polynucleotide chain." Since the claims are all limited to "an oligonucleotide", and since an oligonucleotide is defined in the specification as a single stranded molecule, the only reasonable interpretation for a single stranded molecule that has at least first and second strands is that the claimed oligonucleotides must be single stranded molecules that each contain subregions (corresponding to the first and second strands) that are self complementary and capable of forming a duplex (i.e. a hairpin oligo). However, this is inconsistent with the remainder of the specification's exemplified embodiments, and claims, which disclose the first and second regions as distinct molecules. For example, claim 15 recites an oligonucleotide which has a first and second strand that have a cholesterol molecule attached to their free 5' and 3'-ends respectively. If the interpretation above

holds, then the first and second strands cannot have free 5' and 3' ends, since the first and second strands must be on the same contiguous molecule by specification's definition. If it is applicant's intention to claim molecules comprising first and second strands which are distinct molecules, one remedy may be to claim an "oligonucleotide structure" as recited in the 2nd paragraph of page 2, comprising oligonucleotides, wherein each oligonucleotide corresponds to a first or a second strand. In the interests of compact prosecution, the remainder of this action presumes that the first and second strands, and any other strands, are distinct molecules. However, clarification is required.

Claim 3, and by dependency claim 11, recite "[a]n oligonucleotide according to claim 2 comprising a first strand and a second strand of nucleic acid, said two strands being hybridized to each other in a duplex section in a manner that they first strand terminal end is not a part of said duplex section and free from a hydrophobic anchoring moiety." However, claim 2 recites an oligonucleotide which has hydrophobic anchoring moieties at its terminal ends. Thus, claim 2 requires an oligonucleotide having said moieties at both of its ends, while claim 3 imports these limitations yet requires that the first strand end is free from a hydrophobic anchoring moiety. These limitations are mutually exclusive, and are thus indefinite. Claim 11 is rejected for importing all the limitations of claim 3 while not correcting the noted deficiency.

Claim 4 recites the limitation "said first and second strand " in claim 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 5 recites "[a]n oligonucleotide according to claim 3 comprising n additional strands; n being an integer and n>0; wherein the additional strands are each provided with a terminal hydrophobic anchoring moiety, wherein a first additional strand is hybridized to said

second strand and wherein a second additional strand is hybridized to the first additional strand and strand n is hybridized to strand n-1." It is not clear from this description which strand is being referred to by the claim's reference to "strand n" and "strand n-1", since "n" is defined in the claim simply as an integer, and not the name any specific strand. Correction is required. This claim has not been treated further on the merits due to its indefiniteness.

Claim 9 refers to "the hydrophobic anchoring moiety" to claim 1. However, claim 1 recites at least two such moities, and it is not clear which one claim 9 refers to. The claim is indefinite therefore. Claim 11 has the same problem with a different chain of claim dependencies.

Claim 14 recites "[a]n oligonucleotide according to claim 2, wherein the first strand is longer than the second strand, said first and second strands have a duplex region involving the terminal end of the second strand." However, there is insufficient antecedent basis in claim 2 for "the first strand" or the "the second strand".

Claim 17 recites "[a]n oligonucleotide according to claim 9, wherein the first strand is 30mer DNA; the second strand is a 15mer DNA having 12 complementary bases." However, there is insufficient antecedent basis in claim 9, or claim 1 from which it depends, for "the first strand" or the "the second strand".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3, 9-13, and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Uhlmann et al. (U. S. Patent Number 7,615,539).

The claims are drawn to an oligonucleotide comprising at least two hydrophobic anchoring moieties capable of being attached to a lipid membrane, or wherein said hydrophobic anchoring moieties are located in its terminal ends. The claims also embrace an oligonucleotide comprising at least two hydrophobic anchoring moieties selected from steroids, fatty acids, hydrophobic peptides and lipids, or wherein the hydrophobic anchoring moieties is cholesterol or a derivative thereof.

The claims embrace an oligonucleotide comprising a hydrophobic moiety adapted and available to be linked to a surface immobilized linker or to another lipid membrane attached linker. The claims embrace an oligonucleotide according to the invention which is immobilized to a surface, or which comprises a section of PNA monomers.

Uhlmann et al. teaches a duplexed oligonucleotide, wherein each oligonucleotide is covalently bound to a cholesterol moiety at their terminal ends (see column 19 for example).

Uhlmann et al. teach an oligonucleotide comprising a first strand and a second strand of nucleic acid, said two strands being hybridized to each other in a duplex section in a manner that a first strand terminal ends is not a part of said duplex section and free from a hydrophobic anchoring moiety.

Uhlmann et al. teaches an oligonucleotide comprising a hydrophobic anchoring moiety which is cholesterol and derivatives thereof, and wherein the hydrophobic anchoring moiety is spaced apart from the duplex section by a spacing group or non-hybridized nucleic acid units. See columns 9 and 10 for example. Uhlmann et al. is considered to teach an oligonucleotide comprising at least two hydrophobic moieties adapted and available to be linked to a surface immobilized linker or to another lipid membrane attached linker, since it is well known in the art that the linkers and cholesterol taught by Uhlmann et al. are capable of such adaptation. Uhlmann et al. teaches such oligonucleotides bound to cholesterol in composition with a liposome. The instant specification teaches that such molecules integrate their cholesterol moiety into biological membranes, and since the membrane of a liposome is a biological membrane that is considered to comprise a "surface" in the broadest reasonable sense, Uhlmann et al. is considered to each oligonucleotides with a hydrophobic moiety immobilized to its surface. Uhlmann et al. also teach an oligonucleotide as claimed instantly, further comprising a section of peptide nucleic acids (PNA) capable of forming PNA-peptide complexes.

Claims 1, 2, 4, 9, 10, 12, 13, 14, and 16 rejected under 35 U.S.C. 102(b) as being anticipated by Tyagi et al. (WO 2002/33045, applicant's IDS).

The claims are drawn to an oligonucleotide comprising at least two hydrophobic anchoring moieties capable of being attached to a lipid membrane, or wherein said hydrophobic anchoring moieties are located in its terminal ends, which may be adjacent to each other.

The claims also embrace an oligonucleotide comprising at least two hydrophobic anchoring moieties selected from steroids, fatty acids, hydrophobic peptides and lipids, or wherein the hydrophobic anchoring moieties is cholesterol or a derivative thereof.

The claims embrace an oligonucleotide comprising a hydrophobic moiety adapted and available to be linked to a surface immobilized linker or to another lipid membrane attached linker. The claims embrace an oligonucleotide according to the invention which is immobilized to a surface, or which has a second strand longer than a first, or comprises a section of PNA monomers.

Tyagi et al. teaches a duplexed oligonucleotide, wherein each oligonucleotide is covalently bound to a cholesterol moiety at their terminal ends which are adjacent to each other (see figure 4 for example).

Tyagi et al. is considered to teach an oligonucleotide comprising at least two hydrophobic moieties adapted and available to be linked to a surface immobilized linker or to another lipid membrane attached linker, since it is well known in the art that the linkers and cholesterol taught by Tyagi et al. are capable of such adaptation. Tyagi et al. also teaches such oligonucleotides bound to cholesterol in composition with a liposome. The instant specification teaches that such molecules integrate their cholesterol moiety into biological membranes, and since the membrane of a liposome is a biological membrane that is considered to comprise a "surface" in the broadest reasonable sense, Tyagi et al. is considered to each oligonucleotides with a hydrophobic moiety immobilized to its surface. Tyagi et al. also teach an oligonucleotide as claimed instantly, wherein a first strand is longer than a second, and has a duplex involving the terminal end of the

second strand. (See Example 1 for example), and an oligonucleotide with further comprises a section of peptide nucleic acids (PNA) capable of forming PNA-peptide complexes.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-8, 15, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al. (supra) as applied to claims 1-3, 6, 9-13, and 16 above.

The claims embrace an oligonucleotide comprising at least two hydrophobic terminal moieties at terminal ends, in addition to a first and a second strand, said two strands being hybridized to each other in a duplex region in a manner that leaves the first strand free to hybridize with a third strand, or wherein said first strand has hydrophobic anchoring moieties in both terminal ends, or wherein said third strand has a terminal hydrophobic anchoring moiety so first and third strands have adjacent hydrophobic anchoring moieties.

The invention also comprises an oligonucleotide comprising a first strand of the oligonucleotide that essentially has double the amount of nucleic acid monomers than the second strand, which may have a cholesterol molecule attached to their free 5' and 3'-ends, respectively.

The oligonucleotide of the invention may have a first strand which is 30-mer DNA, and a second strand which is a 15-mer DNA having 12 complementary bases.

Uhlmann teaches oligonucleotides that comprise at least one single stranded region and at least one double stranded region, wherein said oligonucleotide is linked to at least one lipophilic group. This is considered to comprise a teaching of an oligonucleotide that comprises at least one hydrophobic moiety, and that also has a first and second strand hybridized to each other in a manner that leaves the first strand free to hybridize with a third strand, since the embodiment of the prior art that has only one single strand would necessarily be free to bind with a hypothetical third strand. Note that none of claims 6-8 actually require the presence of a third strand, since the claims are drawn to an oligonucleotide that has a first and second strand, wherein the first is available to bind to a third. Uhlmann is that molecule or wherein said first strand has hydrophobic anchoring moieties in both terminal ends, or wherein said third strand has a terminal hydrophobic anchoring moiety so first and third strands have adjacent hydrophobic anchoring moieties. Uhlmann does not teach an oligonucleotide that has at least two hydrophobic moieties at terminal ends that also has a strand free to hybridize to another strand.

However, such an oligonucleotide would have been obvious to one of ordinary skill in the art the time the invention was made, since Uhlmann teaches the use of two lipophilic moieties in the paragraph following his teaching of an oligonucleotide that has a free region for binding a third strand. Although Uhlmann does not state that the lipophilic moieties should go at the terminal ends, there are only a finite number of choices, and arriving at this configuration would be considered to result from routine optimization with a reasonable expectation of success. The same is considered to be true for claims 15 and 17, which are drawn to

oligonucleotides having double the number of monomers in one strand compared to the second strand, or specifically have 30 monomers in one and 15 in the second. Uhlmann et al teaches oligonucleotides having at least one region of double strandedness and at least one region of single strandedness. Although Uhlmann does not provide the length of these specific molecules, he does teach that a preferable length is 15-30 nucleotides. Since it would be apparent to one of ordinary skill that a molecule having both single- and double-stranded regions are also going to differ in the number of nucleotides present in each, one of ordinary skill in the art would have considered it within the bounds of routine optimization to arrive at a molecule that has 15 nucleotide monomers on one strand and 30 on another, given that Uhlmann teaches oligonucleotides having at least one region of double strandedness and at least one region of single strandedness, and since 15-30 is considered by Uhlmann to be an optimal range. Accordingly, in the absence of evidence to the contrary, one of ordinary skill in the art would have considered the invention to have been prima facie obvious at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James (Doug) Schultz, PhD whose telephone number is (571)272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James (Doug) Schultz, PhD/
Primary Examiner, Art Unit 1633